Pharmacology of carbon dioxide

By Alex Yartsev - 12/06/2015
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This chapter is related to the aims of Section F10(ii) from the 2023 CICM Primary Syllabus, which expects the exam-going trainees to be able to "*explain the physiological effects of ...hypercapnia and hypocapnia.*" In the exam, this has come up at least once, in Question 21 from the second paper of 2012 where the exam candidates were asked to *"describe the physiological consequences of a progressive rise in blood carbon dioxide levels."* In effect, this describes the dose-response relationship of CO_2, and consequently, this chapter treats CO_2 as one might treat a drug. The discussion revolves around its physicochemical properties, relevant features of its transport in the body, and most importantly the physiological effects of hypercapnia and hypocapnia. For the CICM answer, the college also expected *"a mechanistic description the neuro-cellular events"*, which apparently meant some discussion of the ventilatory responses to CO_2, something which is discussed in more detail in the chapter on the relationship of arterial carbon dioxide and alveolar ventilation.

In summary:

The physiological consequences of hypercapnia are:

- Depressed airway reflexes with severe hypercapnia
- Changes in respiratory drive:
  - Increased respiratory drive with mild hypercapnia
  - Depressed respiratory drive with severe hypercapnia
  - These changes are controlled by central chemoreceptors
  - The chemorecetors are sensitive to changes in the pH of CSF
  - Their output is maximal with a PaCO2 of 60-65 mmHg
  - With extremely high PaCO2, the neurodepressant effect of hypercapnia actually depresses the respiratory drive
- Changes in respiratory function:
  - Bronchodilation
  - Right shift of the oxygen-haemoglobin dissociation curve

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    - Sympathetic overactivity, thus:
    - Hypertension
    - Tachycardia
    - Serum catecholamine excess
    - Increase in cardiac output
    - Prolonged QT interval
- Vasoactive effects:
    - Systemic arterial vasodilation
    - Pulmonary arterial vasoconstriction
- CNS effects
    - Progressively increasing sedation
    - Increased intracranial pressure
- Acid-base effects
    - Acidosis
    - Increased serum bicarbonate
- Other organ system effects
    - Increased renal vascular resistance
    - Decreased GFR
    - Decreased urine output
    - Increasd portal venous pressure and vascular resistance

In terms of published material, the best peer-viewed article is probably the chapter by Servillo et al (2001), but it is unfortunately paywalled by Springer.

Chemical properties and molecular structure

First, let's meet the gas.

CO_2 is a single carbon atom attached to two oxygen atoms by double covalent bonds, which makes it a rather nonpolar molecule. It sublimates at around -78℃, and has a bunch of other interesting properties, not the least of which is its behaviour as a supercritical fluid. Fortunately or unfortunately, this sort of thing is never seen in the ICU.

- **Melting Point : -55.6° C**
- **Boiling Point : -78.5° C** (at this temperature, it sublimates at atmospheric pressure)
- **Density : 1.977**

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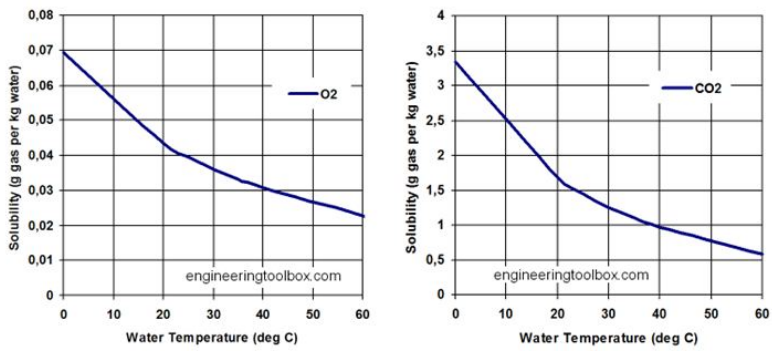
In aqueous solution, CO_2 acts as a Lewis acid, spontaneously (and slowly) hydrating and producing carbonic acid (H_2CO_3). At normal physiological pH, the equilibrium point of this reaction strongly favours CO_2 over H_2CO_3, and therefore in body fluids most of the CO_2 molecules will be found as a dissolved gas. Greater detail regarding the solubility and hydration of CO_2 is available in the chapter concerning the transport of CO_2, and buffering of acute respiratory acid-base disorders.

Like most gases, the solubility is influenced by temperature. As the temperature decreases, more CO_2can dissolve in water, and this can be demonstrated in carbonated beverages (which "out-gas" as they warm up). CO_2 is more soluble in water than oxygen; substantially so (just see these temperature -vs-solubility graphs pirated from engineeringtoolbox.com).



At 37℃, in every litre of pure water one can find perhaps 1g of dissolved CO_2, and about 0.033g of O2.

Chemical Relatives

Other gaseous dioxides probably belong in this category, but it is not particularly meaningful to treat them as the chemical relatives of CO_2. Their chemical properties are starkly different. NO_2 is also a molecule which features two double-bonded oxygen atoms, but its bonds are at an angle, and it has an unpaired electron which makes it a free radical. Like sulphur dioxide (SO_2) it is a pungent-smelling toxic gas. It is fair to say that chemically CO_2 is without peer.

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Administration and absorption

Another side-effect of treating CO_2 as a drug, the "administration and absorption" section is somewhat artificial. One does not usually find a clinical need to administer this gas. Our patients generate enough of it as it is.

Anyway, absorption of CO2 occurs rapidly through the alveolar wall. Its excellent water and lipid solubility permit it to diffuse readily through this short distance, and it is exchanged more easily than oxygen in the lungs. This exchange is typically one-way, as atmospheric gas (largely representative of fresh alveolar gas) typically contains very little CO_2 (0.027-0.036%), and the concentration gradient favours the movement of CO_2 out of the alveolar capillary blood and into the alveolus. The absorption of CO_2 through the peritoneum or gut wall is much slower, as will be discussed below; however, these can also be viewed as methods of administration.

Metabolism and clearance

Though it is not metabolised in any conventional sense, CO_2 undergoes chemical changes in the bloodstream. Specifically, its transport in the blood resembles metabolism, in the sense that the natural hydration reaction (which converts CO_2 into H_2CO_3) is vigorously catalysed by carbonic anhydrase in the red blood cells, with H^+ and HCO_3^- the end products. This "metabolic process" is discussed in greater detail in the chapters on the physiology of CO_2 transport and the buffering of acute respiratory acid-base disorders.

Respiratory clearance of CO_2

Clearance of CO_2 is almost 100% dependent on alveolar ventilation. It is added to the alveolar gas mixture by the capillaries and exchanged with the atmosphere by respiration. The exchanged amount might appear relatively small; Nunn's textbook quotes a mixed venous CO_2 of 46 mmHg, and an arterial CO_2 of 40mmHg, meaning that only a paltry 6mmHg fall in partial pressure occurs in the pulmonary circulation. However one must remember that a major portion of CO_2 is transported in the blood as bicarbonate and

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carbamates. In the capillary blood, the carbonic anhydrase in erythrocytes catalyses the reverse reaction, converting carbonic acid back into CO_2 and water, restoring volatility to the stored CO_2. The actual amount of cleared CO_2 is closely related to whole-body energy expenditure and metabolic substrate oxidation, and therefore to oxygen consumption. In fact, the relationship between oxygen consumption and CO_2 elimination is widely known as the Respiratory Quotient and is discussed in greater detail in the chapter concerning indirect calorimetry.

Cutaneous clearance of CO_2

In addition to the splendidly evolved process of respiration, we land mammals can also eliminate small quantities of CO_2 via our skin, outlandishly amphibian though this may seem. Rather like the amphibians, the quantity of "perspired" CO_2 is dependent on the amount of skin water, and wet sweaty skins seem to promote its clearance by this route. Or rather, the administration of atropine to a bunch of healthy volunteers locked in whole-body plethysmographs seems to diminish the rate of cutaneous CO_2 clearance by decreasing sweat production. The mechanism was thought to be direct diffusion (given the complete lack of any dedicated mechanism), reliant on the fact that CO_2 seems to diffuse into all body fluids equally, and is therefore also present in sweat.

No matter the wetness of one's sweaty hide, its performance as a gas exchange organ is very poor: the sweatiest volunteers in the above-linked study (they were males) excreted a maximum of 1.43ml/min of CO_2 per every smelly hairy square metre of their bodies. At this rate, it contributed about 0.5% of the total clearance rate for these subjects. Studies involving only moistened muscular extremities such as the human upper limb (and noting the effect of exercise thereupon) have managed to increase this rate to 9.1ml/min/m^2, albeit locally and only for brief periods.

Without any further digression, one can summarise by saying that CO_2 is eliminated at a rate proportional to alveolar ventilation.

Intentional and unintentional exogenous CO_2 administration

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If one were discussing CO2 as a drug, one would include a section on indications and contraindications. However, in the absence of actual indications, it would probably be more proper to discuss the use of exogenous CO_2 as intentional and unintentional.

Accidental exogenous CO_2 exposure

The favourable capillary-atmospheric CO_2 concentration gradient is merely the byproduct of living on a planet capable of sustaining life. One can envision scenarios where one might find oneself in a confined environment with a locally increased atmospheric concentration of CO_2. Say, one is at the bottom of a poorly ventilated mineshaft (considering that CO_2 is heavier than air, and readily sinks to the bottom). Or, one finds oneself using a CO_2-based fire extinguisher in a garage where a small controlled oil fire has become less small and less controlled. Or one's laboratory has lost power in a warm summer storm, and the dry ice freezer has explosively sublimated. It is possible to imagine numerous scenarios in which you will inevitably get a snootful of carbon dioxide. In such a case, the laws of diffusion will turn on you. The excess CO_2 in the inhaled gas mixture will diffuse readily into the blood, giving rise to acute carbon dioxide poisoning.

Pneumoperitoneum as a source of exogenous CO_2

More frequently than weird laboratory accidents, the source of excess CO_2 is a surgical procedure. Because of its excellent solubility and rapid absorption, CO_2 is an ideal gas to use as an insufflation medium for laparoscopic procedures. Without digressing on the added effects of hypothermia and mesenteric dehydration (resulting from insufflation with cold dry gas) one can summarise that having one's viscera inflated like a balloon is an intensely abnormal experience, and hypercapnea is only one of the many physiological derangements which develop as a consequence, but let it be the focus of discussion for the present moment.

In this situation, one's peritoneal cavity becomes the gas exchange surface. Needless to say it is not well adapted to this purpose, and the gas exchange takes substantially longer (the membranes are thicker and the blood flow poorer). Generally, after insufflation it takes 15-30 minutes for the arterial [illegible] but the level climbs gradually thereafter and

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seems the longer the procedure the more CO_2 ends up in the arterial blood.

Similarly, the insufflation of the bowel with several litres of CO_2 during endoscopy can result in the absorption of CO_2 though the gut wall.

However, the iatrogenic hypercapnea of laparoscopy is not so much an indication for CO_2administration, but rather an unwanted consequence of wanting to see the organs better with your camera. There are few existing indications for adding CO_2 to a patient's gas mixture.

Historical indications for the administration of exogenous respiratory CO_2

In the distant past, CO_2 inhalation was used to treat a variety of disorders. A 1957 article from the*American Journal of Psychiatry* remarks upon its *"favorable effects in a variety of neuroses and psychosomatic conditions, especially in anxiety states, phobic reactions, certain ill defined tension states, and conditions like spastic colitis and migraine headaches"*. With enviable attachment to scientific fact, the author (Dr. Moriarti) proposed that the mechanism of action consists of the*"breaking up of pathologic reverberating circuits in the nervous system"*.

Modern uses of medical CO_2

Though these days no qualified medical professional makes any further sincere attempts to therapeutically half-asphyxiate their patients, medicinal CO_2 has found other uses. For instance, its cutaneous use has been proposed as a means of improving microcirculation in chronic wounds. In precritical times CO_2-rich fumarole springs were well-known solutions to peripheral arterial spasm resulting from ergot poisoning, and this has been revived in modern-day management of surgically untreatable claudication. Furthermore, it has found widespread pseudoscientific use as a part of bullshit "therapies" like Spirovitalisation.

Effects of hypercapnea and their mechanisms

Though it is difficult, some attempt will be made here to artificially divorce the effects of the acidosis which accompanies it.

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This is probably impossible. For instance, the anaesthetic effect of CO_2 is likely totally reliant on the intracellular acidosis which develops in hypercapnia, and so the two cannot be separated.

Increased respiratory drive with mild hypercapnea

Mild hypercapnia increases "respiratory drive" as a homeostatic mechanism which defends the acidity of your body fluids.

In the interest of preserving reader sanity, an extensive digression regarding the respiratory drive will not be carried out here (because that happens elsewhere). Instead, I will refer the curious to Hans Loeschcke's masterpiece from 1981, "*Central chemosensitivity and the reaction theory*". In summary, Loeschcke discusses a series of elegant experiments (some performed by himself and colleagues, many decades earlier) involving anaesthetised cats having their subarachnoid spaces accessed and irrigated with solutions of varying pH and pCO_2. The authors had reached a conclusion, that "*the extracellular pH in the brain is the main chemical signal determining ventilation.*"

Generally speaking, the respiratory drive response to a respiratory acidosis is greater than the response to a metabolic acidosis with the same pH. This is because the medullary respiratory control centre resides within the blood-brain barrier. CO_2 is able to penetrate this barrier easily, whereas hydrogen ions cannot.

For the hypercapnia-naive person, the maximum respiratory stimulant effect of CO_2 is achieved at about 100-200mmHg. There is quite a broad range reported. For instance, Nunn's quotes 100-200mmHg as the maximum value. ANZICS guidelines for apnoea testing (in the context of the diagnosis of brain death) suggest that a pCO_2 of over 60mmHg is "adequate stimulus", alternatively represented as a 20mmHg rise from a baseline, or a drop to a pH of around 7.30.

This 55-60mmHg level also seems to be the CO_2 level at which most normal people will terminate their voluntary breath hold. The linked article is a study of volunteer breath holders; the maximum effort seems to have been 135 seconds, at the end of which the volunteer was probably quite blue, with a

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Decreased respiratory drive with severe hypercapnia

Beyond the "maximal" ventilatory drive stimulus at 100-200mmHg, hypercapnia tends to depress and ultimately abolish the activity of respiratory control centres. At least that is what all the influential textbooks say. How do they know this? Experience, experiment, mushroom-induced trance revelation?

It is uncertain. No references regarding this are available in Nunn's, even though Nunn's can usually be counted on for some hardcore physiology data.

Anyway. This respiratory depression in extreme hypercapnia is probably a function of its anaesthetic effects, which are described below. After all, 200mmHg or more of pCO_2 represents an $FiCO_2$ approaching 30%, which seems to be the threshold of unconsciousness for large mammals. Similarly to its overall neurodepressant effect, this respiratory depression can probably be blamed on the neuronal intracellular acidosis which develops in severe hypercapnia.

Bronchodilation

Yes, CO_2 seems to be a bronchodilator. In a series of patients (some of whom had COPD and asthma) a state of normoxic hypercapnia resulted in significant measurable changes in airway resistance. This is probably an effect mediated by the general state of smooth muscle relaxation, which is discussed elsewhere. van den Elshout et al (1991) suggests that there may be no direct effect on the smooth muscle of the bronchi as such (as studies of disembodied bronchi have shown that the bronchial smooth muscle either dilates, constricts, or stays unchanged in response to CO_2). It seems more likely that the effect is mediated by central medullary chemoreceptors, sending a signal to the bronchi, commanding them to dilate. This would make sense - i.e. more airway calibre means less airflow resistance and therefore better CO_2 clearance, which seems like an adaptive response.

Right shift of the oxygen-haemoglobin dissociation curve

Elsewhere, a lively discussion of the factors which influence the oxygen-haemoglobin dissociation curve makes mention of this effect. CO_2 improves the stability of deoxyhaemoglobin, thereby enhancing its affinity for CO_2 and

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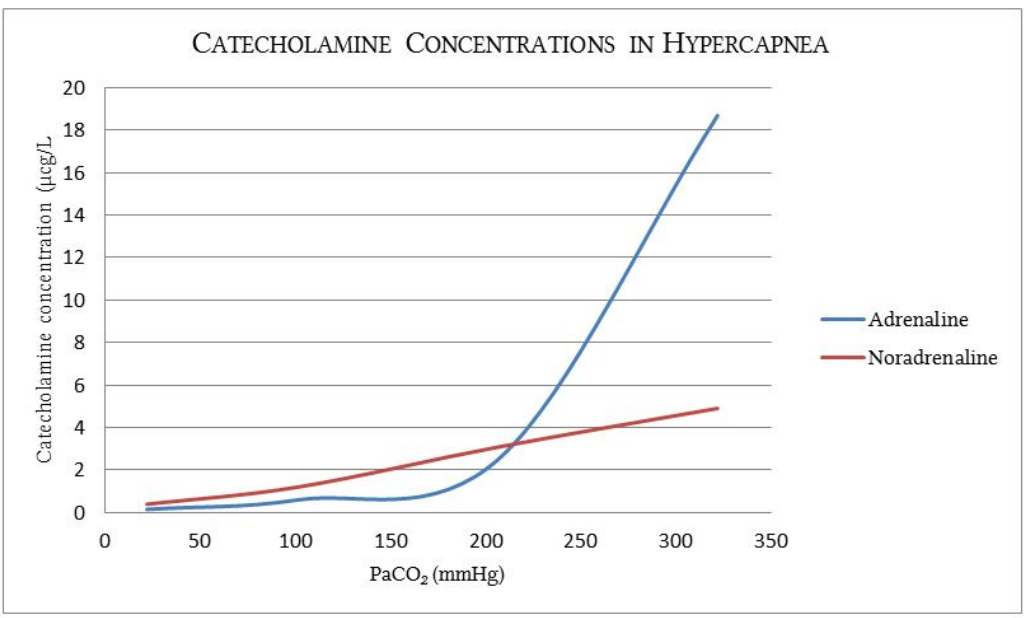
city of blood (by allowing some CO_2 to be

stored in the haemoglobin molecule as carbamates). The effect of pH on the oxygen-haemoglobin association mechanics is far greater than the effect of CO_2, but usually, acidosis and hypercapnia occur together, and this issue can be safely ignored. In short, if anybody asks, hypercapnia causes a right-shift of the curve.

Sympathetic stimulation and catecholamine excess

Nunn's textbook refers to a famous 1960s paper by R.A Millar, "Plasma adrenaline and noradrenaline during diffusion respiration." The paper reports on a series of experiments which were performed upon dogs anaesthetised with thiopentone and suxamethonium. The dogs were ventilated by "diffusion", that is to say relying on the mass transfer of O_2 being entrained through a patent airway. As the apnoea went on, so their arterial CO_2 climbed ever higher. The investigators collected samples and measured the $PaCO_2$, noradrenaline and adrenaline concentrations.

This is what Millar's beautiful data looks like if you feed it into the grinder of MS Office:



Thus, the ridiculous acidotic environment of extreme hypercapnia tends to produce a massive catecholamine storm.

The effects of this are somewhat offset by the fact that in acidosis of this magnitude, the catecholamine receptors are unlikely to be binding much of

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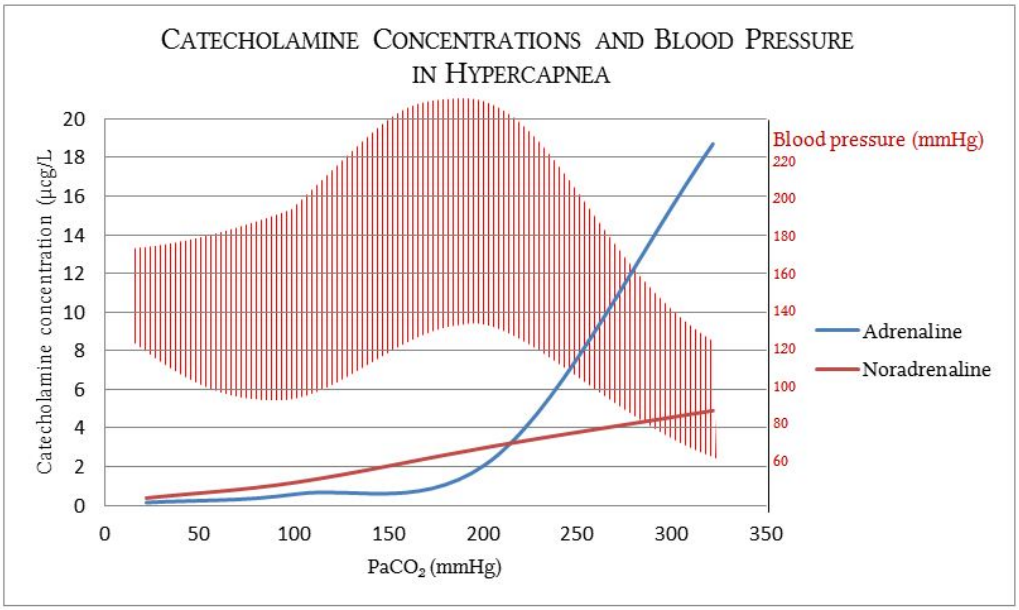
comes more prominent as the acidosis

worsens, and the catecholamine receptors become less responsive. Indeed, Millar included measurements of blood pressure in his dog experiments, which demonstrate this feature.



As one can plainly see, the initial stages of hypercapnea (in the "usual" range, from normal to about 100mmHg) are characterised by a fall of diastolic and a moderate increase in systolic pressure. Then, as $PaCO_2$ rises the blood pressure increases, up to a plateau at some point around 200mmHg $PaCO_2$. After this plateau, the acidosis (and probably the β-2 receptor effects of adrenaline) results in a fall of blood pressure.

The excess catecholamines seem to come from the adrenal glands, perhaps without any influence from the sympathetic nervous system. In a weird twist, rats with denervated adrenal medulla enjoyed a normal catecholamine response to hypercapnia (but not hypoxia, which seems to be mediated by sympathetic reflex arcs between the carotid bodies and the adrenal glands). In short, one's adrenal medulla will continue pumping out catecholamines in response to a raised CO_2regardless of what else is happening in the autonomic nervous system.

Why does this happen? What is the point of activating the sympathetic nervous system in advanced near-anaesthetic stages of hypercapnia? It almost appears counterproductive; surely evolution would favour such organisms that respond to asphyxia by decreasing their metabolic activity, [illegible] body mass.

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Perhaps this catecholamine surge is actually a redundant autonomic reflex, which has persisted in some form since the middle Palaeozoic aeon. Fish appear to have a stereotypical stress response triggered by hypoxia and hypercapnia, which results in a potent pro-respiratory catecholamine surge, resulting in such life-preserving maneuvers as the mobilisation of red blood cells from the spleen. In humans, this excess of sympathetic activity may represent an attempt to counteract or compensate for the cerebral vasodilation which occurs in response to a high CO_2. This would be a great hypothesis if it were supported by any evidence whatsoever, but in fact, the sympathetic nervous system may have little control over cerebral vessels. In short, no satisfactory explanation of the *purpose* behind this phenomenon could be found during a half-hour of lazy Googling, and I would gladly hear any suggestions to expand this area.

Depression of cardiac contractility …but with an increase in cardiac output

Yes, hypercapnia is supposed to have a direct depressant effect on the myocytes. In fact, acidosis is also supposed to have this effect, and together these two should produce an impressive degree of heart failure. However, there is also the sympathetic excess mentioned above. And on top of that, there is the fluctuation in catecholamine receptor sensitivity which occurs with acidosis. In short, the net effect of hypercapnia on the cardiovascular system is rather unpredictable.

Pulmonary vasoconstriction

Respiratory acidosis certainly seems to cause pulmonary vasoconstriction, and hypocapnia seems to reverse the positive effects of pulmonary hypoxic vasoconstriction. However, there is good evidence that these effects are related more to the pH rather than to the p CO_2. Therefore, this aspect is discussed in greater detail elsewhere

Anaesthesia

Yes, CO_2 has anaesthetic properties, which permits us to treat it as an anaesthetic gas for the purporses of discussion. Given the ethical quagmire of intentionally exposing human subjects to high concentrations of an obviously [illegible] data regarding the anaesthetic potency of

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CO_2 comes from animal studies. For instance, rats. In the rat an extrapolation from CO_2-induced changes in the MAC values of inhalational anaesthetics had revealed that the MAC of CO_2 was approximately 50% at 1 atmospheric pressure, giving an $FiCO_2$ of around 380mmHg.

$PaCO_2$ of 380mmHg. Let us just think about that for a second.

Those 380mmHg of gas are not sitting around in the bloodstream being politely inert. It is *influencing your pH*. In fact, if we use the "1 for 10" Boston rule together with the Henderson-Hasselbach equation, we end up with serum bicarbonate of around 58mmHg, and a pH around 6.805, which cannot be benign in terms of ongoing cardiovascular survival.

Thus, surely you would die purely from the acidosis if you were a rat and your $PaCO_2$ was 380mmHg.

Indeed - the above-linked rat study mentions that those sorts of concentrations were uniformly fatal.

So how much $PaCO_2$ do you require to become unconscious, but *not die?*

Again we turn to animal studies. Let us use a larger mammal this time.
An ancient manuscript from the 1950s detailing the effects of hypercapnia on mongrel dogs gives us some data regarding the survivability of extreme hypercapnia. Of the dogs, those exposed to around 35% $FiCO_2$ (266mmHg) all survived; of those receiving 45% $FiCO_2$ half were dead within 90 minutes.

These animal data agree with human case reports. An even more ancient manuscript, reporting studies on even larger mammals (*humans*) reports that a concentration of around 30% were required for a reversible EEG waveform flattening. Similarly, a BMJ article reports on a case of "extreme" hypercapnia with a $PaCO_2$ of around 232mmHg, and a pH of around 7.00 - at this level, the GCS was 3 and the patent required intubation. Indeed, 30% of 760 is actually 228mmHg, which is very close to the $PaCO_2$ from the case report.

So, now that we are exploring the dangerous depths of CO_2 narcosis, the question arises: how deep can you go, and then *come back*? The upper limits of survivable hypercapnia are reported in an often-quoted article which details the survival of a patient following a massive grain aspiration (it was wheat).

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so proud of this case report that they offer it

for free. The patient in question was a 16-year-old 65kg boy who fell (and was immediately subsumed) into a wagon being filled with grain. It took them five or so minutes to get him out. This poor lad survived a shocking $PaCO_2$ of 501mmHg, the highest ever reported in a surviving patient. He managed to get through his ordeal despite having essentially no lower airway (indeed, the authors complain that after extensive laryngoscope-assisted debulking of the upper airway grain mass, the boy's ETT could not be advanced beyond his larynx "*probably due to impacted grain in the trachea*").

The upper limits of $PaCO_2$ which are still consistent with normal cognition were inadvertently explored by one COPD patient who astonished nearby physicians by remaining "awake and alert" with a $PaCO_2$ of 160mmHg. This case demonstrates that potentially some sort of conditioning occurs in chronic hypercapnia, which may protect you from CO_2 narcosis.

This conditioning may well be related to the concentration of bicarbonate in the cerebrospinal fluid. The major mechanism of CO_2 narcosis appears to be closely related to the development of neuronal intracellular acidosis. In fact, Nunn's textbook reports (on the basis of this dog study) that the degree of narcosis correlates more closely with cerebral pH than with arterial pCO_2.

In addition to the abovementioned "direct" anaesthetic effects, "extreme" hypercapnia may also cause unconsciousness by impairing cerebral autoregulation, allowing too much blood flow into the brain and thereby increasing intracranial pressure.

Influence of CO_2 on cerebral blood flow and "intracranial steal" phenomena

Hypercapnea tends to increase cerebral blood flow by a fairly large degree. A wonderful review article from Anesthesiology (1998) allows the enthusiast to wallow in luxurious detail. The process is complex, and furthermore, the mechanisms are different between neonates and adults.

It seems the CO_2 influences cerebral vessel diameter by the following mechanisms:

- Change of periarteriolar pH leads to a change in nitric oxide synthase activity;
- Nitric oxide synthase catalyses intracellular cGMP production;

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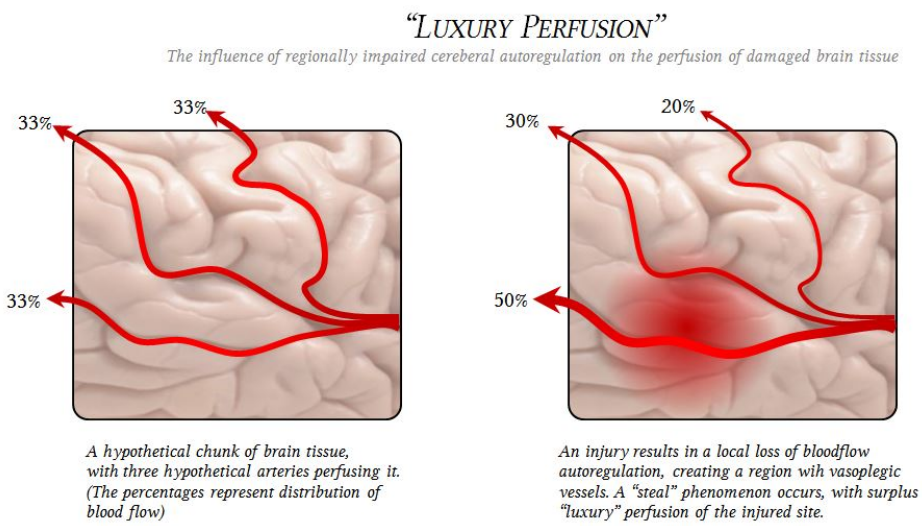
- cGMP acts as a second messenger to affect a change in intracellular ionised calcium availability.

Nunn's quotes some figures for precisely how the pCO_2 influences cerebral blood flow. Apparently, there is a 1-2ml increase in blood flow for every 1mmHg change in pCO_2 (this is blood flow in terms of ml per 100g of brain tissue, per minute). This figure seems to be borrowed from a 1970 paper co-authored by the famous Plum and Posner (authors of the famed "stupor and coma" textbook).

Irritatingly, this mechanism appears to be lost in damaged brain tissue. That tissue then becomes vasoplegic, its vessels flaccid and paralysed, unable to autoregulate blood flow. The result is the so-called "luxury perfusion" phenomenon.



This gives one reason to wonder as to why we care so much about CO_2 in traumatic brain injury.

If the CO_2 responsiveness of cerebral vessels is lost, then surely does not matter what the pCO_2 is? The patient's pCO_2 levels could fluctuate wildly, but their cerebral perfusion would remain the same, right?

As it turns out, this is not the case.

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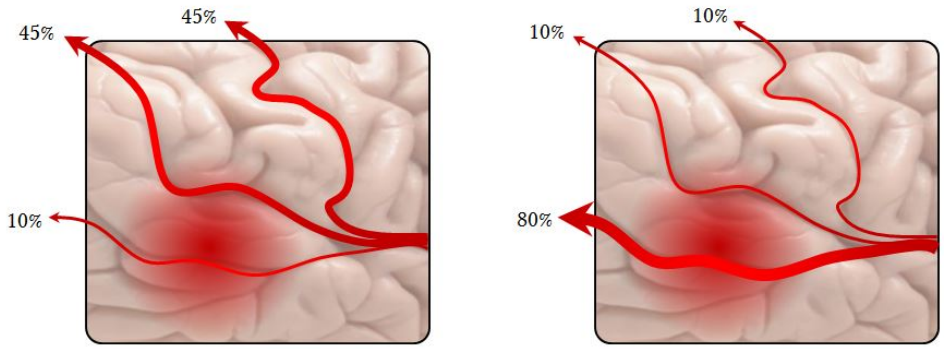

SYSTEMIC HYPERCAPNEA:
The undamaged CO_2-responsive vessels vasodilate and "steal" a major portion of the bloodflow from the damaged area, worsening local ischaemia near the injury

SYSTEMIC HYPOCAPNEA:
The undamaged CO_2-responsive vessels vasoconstrict; blood flow is diverted into the vasoplegic vessels, pathologically increasing the blood flow into the injured area, and causing worsening local pressure effects and oedema

In the absence of CO_2 responsiveness, perfusion of this damaged tissue then becomes dependent on the responses of the surrounding tissue. If the surrounding tissue is subjected to hypercapnia, the vessels with intact autoregulation will vasodilate, diverting blood flow away from the damaged area (creating local ischaemia). Conversely, in hyperventilation, the low CO_2 levels will cause the still-responsive vessels to constrict, diverting excess blood into the damaged parenchyma, causing increased local pressure effects, worsening oedema, and other neurosurgically worrying effects.

And that is why we worry about CO_2 in the traumatic brain injury patients.

Decreased systemic vascular smooth muscle tone

As it dilates the cerebral vessels, so CO_2 relaxes all other smooth muscle vascular beds. Richardson et al (1961) elegantly demonstrated that this effect is usually well-suppressed by the general excitatory sympathetic activity. While breathing an $FiCO_2$ around 7%, their volunteers had an unchanged blood flow in their extremities; however, when sympathetic vasoconstrictor signals to their forearm were selectively blocked by phenoxybenzamine there was a 28% change in forearm blood flow, all due to a decrease in peripheral vascular resistance.

However, in the circulatory system unmolested by sympathetic blockade, this vasodilator effect is generally obscured. The net haemodynamic effect of hypercapnia is still hypertension rather than vasoplegia. Kiely et al (1996) demonstrated this in a cohort of normal adult humans whose end-tidal

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mmHg by rebreathing of expired air. SVRI did

not change very much (l,102±38 vs 1,162±78 dyne-s-cm^{-5}) but MAP increased by an average of 10 mmHg, mainly because the cardiac output increased from 5.5 to 7.5 L/min.

Prolonged QT interval and increased propensity towards arrhythmias

CO_2 is a weak elongator of QT intervals. This was also demonstrated by Kiely et al (1996). The change of QT duration in their patients (whose hypercapnia was quite mild) was from 411 to 428 ms on average, which is a good example of a study result which achieves statistical but not clinical significance. It is uncertain what effects on the QT interval would develop due to truly heroic hypercapnia, but truly absurd CO_2 values are often reported in the literature without being mentioned in connection with extreme QT prolongation or polymorphic VT arrest. With that said, Sarubbi et al (1997) demonstrated that QTc *dispersion* is significantly affected by hypercapnia. This is a measure of heterogeneity in cardiac repolarisation, something which is viewed as a marker of ventricular electrical instability.

Electrolyte and acid-base effects of hypercapnia

Hypercapnia has predictable acid-base effects, which give rise to predictable compensatory changes in renal solute handling. In summary:

- Acidosis develops:
  - CO_2 dissolving in the bloodstream produces an acidosis
  - This is because CO_2 combines with water to form carbonic acid
  - This lowers the serum pH
- Serum bicarbonate increases:
  - Because carbonic acid dissociates into H^+ and HCO_3^-
- Renal ammonia and chloride excretion increases
- Renal reabsorption of bicarbonate increases
- The net effect is a renormalisation of serum pH

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Other renal effects of hypercapnia

Unlike the rest of the systemic arterial circulation (which vasodilates with hypercapnia) the effect of severe respiratory acidosis on the renal arteries is vasoconstriction. Bersentes et al (1967) demonstrated this in a dog model. Essentially, the renal vascular resistance doubled when CO2 increased from 40 mmHg to 100 mmHg. This was associated with some decrease in GFR and urine output.

Hepatic effects of hypercapnia

In the liver, high CO_2 in the portal venous circulation causes increased portal venous resistance and decreased portal venous blood flow. Gelman & Ernst (1977) were able to demonstrate this in an animal model. The investigators infused blood with a high CO_2 and low pH into the ligated portal vein and remarked that for every 0.1 decrease in pH, the portal venous resistance increased by about 20%. The authors interpreted this reaction as a logical step taken by an organ which does not want to be perfused with toxic aid blood, bubbing over with carbon dioxide.

Previous chapter: Causes and physiological effects of hypoxaemia

Next chapter: Pharmacology of nitric oxide

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